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Palladium-Catalyzed Cross-Coupling of Silyl Electrophiles with Alkylzinc Halides: A Silyl-Negishi Reaction

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Abstract

We report the first example of a silyl-Negishi reaction between secondary zinc organometallics and silicon electrophiles. This palladium-catalyzed process provides direct access to alkyl silanes. The delicate balance of steric and electronic parameters of the employed DrewPhos ligand is paramount to suppressing isomerization and promoting efficient and selective cross-coupling.

Graphical abstract

Alkyl silanes have a multitude of applications in basic science, medicine, and industry.¹ The subtle steric, electronic, and spectroscopic differences between carbon and silicon are ideal for studies in bi-ostereoisomerism.² Small silicon-containing molecules are used as additives in rubber manufacturing (such as automobile tires), and silahydrocarbons are used as cryogenic fluids and as lubricants in aerospace applications due to drastically altered phase properties compared to their carbon analogues.³ Thus, methods to install a silicon atom with various substitution patterns in a rapid manner can have significant impact across a range of disciplines.

Syntheses of alkyl silanes have been reported for over a century. Historically, hydrosilylation has been a workhorse reaction for the synthesis of *n*-alkylsilanes.⁴ However, hydrosilylation often encounters issues of isomerization and regioselectivity with 1,2-disubstituted olefins.⁵ Arguably, the most attractive method for preparing alkyl silanes is the alkylation of widely available silyl electrophiles with equally abundant organometallic nucleophiles (Figure 1, top). Unfortunately, these reactions suffer from low yields, long reaction times, and

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Supporting Information

Experimental procedures and spectral data. This material is available free of charge on the ACS Publications website.

Notes

The authors declare the following competing financial interests: UD has obtained a provisional patent related to this methodology.

significant side reactions.⁶ Alkylations with primary and aryl nucleophiles are known.^{7,8} As has been recently noted, the addition of secondary organ-ometallic reagents to silyl electrophiles is rarely effective.^{9,10} In fact, to our knowledge, over the past seventy years only five isolated examples with secondary nucleophiles have been reported in the chemical literature.¹¹ This is due to lack of reactivity or competitive reductive processes with these more sterically demanding and electron-rich nucleophiles. Prior catalytic methods, which have proven effective with primary and aryl nucleophiles, are ineffective in coupling secondary alkyl groups.^{6a, 7–8}

In an effort to circumvent this poor reactivity, the Fu and Oestreich groups have independently reported the cross-coupling of silyl nucleophiles and carbon electrophiles (Figure 1, middle).^{9, 12} While these are highly valuable transformations that allow access to secondary alkyl silanes, they rely on nucleophilic silicon reagents, the umpolung reactivity of naturally electropositive silicon. Since silyl electrophiles are the main feedstock of silicon reagents,^{1c} developing a general method of alkyl silane synthesis from these abundant and cheap starting materials is highly appealing.

With this goal in mind, and in the context of our group's standing interest in activation of silicon electrophiles,¹³ we envisioned a catalytic cycle represented in Figure 2. In analogy to the venerable Negishi reaction,¹⁴ oxidative addition of palladium(0) complex **A** into a silyl iodide would generate intermediate **B**. Transmetalation with an alkyl organ-ometallic reagent to form **C**, followed by rapid reductive elimination, leads to the desired alkyl silane and regeneration of the catalyst. As noted in previous studies, a long-standing problem in cross-coupling of secondary C(sp³)-hybridized organometallics is competitive rearrangement to the linear isomer via β -hydride elimination.¹⁵ In this case, the equilibrium between **C** and **D** would be the key component of the catalytic cycle to control.

Due to the greater stability and functional group tolerance compared to other alkyl nucleophiles, we chose to focus our initial studies on the use of alkylzinc halides.¹⁶ As a model system, we investigated the reaction of isopropylzinc iodide with dimethylphenylsilyl iodide in the presence of a palladium catalyst (Table 1). The reactions were monitored both for desired *sec*-alkyl product **1**, as well as isomeric product **2**.

Control experiments without catalyst showed no product formation (Table 1, entry 1). Initial catalytic experiments were conducted with a catalyst derived from Pd₂dba₃·CHCl₃ and PPh₃ (entry 2). Although we were very pleased to observe alkylation product, the yield of **2** was low and modest levels of undesired isomer **2** were observed. Et₃N was identified as an additive that both improved yield and suppressed isomerization (entry 3).¹⁷ The choice of precatalyst was also important, with [allylPdCl]₂ proving superior to Pd₂dba₃·CHCl₃ (entry

4). We attribute this difference to the competitive non-productive ligation of dba to the metal center.¹⁸ We next investigated the nature of the ligand in the reaction. Increased steric bulk in (*o*-tol)₃P (entry 5) resulted in a large decrease in yield. In contrast, the isomeric ligand (*p*-tol)₃P (entry 6) led to an increase in overall yield and reduced isomerization below GC detection limits. Electron-deficient ligands greatly reduced the yield and increased isomerization (entry 7). Under the hypothesis that increased electron density would further improve the yield, we investigated (*p*-MeOPh)₃P (entry 8). While this ligand achieved comparable results to (*p*-tol)₃P, further investigation revealed that reactions using this ligand proved inconsistent with respect to yield and selectivity. We attribute this to ligand instability under the Lewis acidic reaction conditions.¹⁹

In an attempt to avoid ligand decomposition, we turned our attention towards the electron-rich Ar₂P^tBu scaffold, which has been used successfully in silyl-Heck reactions.^{13a, 13b} The parent ligand (Ar = Ph, entry 9) produced only moderate yield along with significant isomerization. However, with the larger and more electron-rich JessePhos (**L1**), we observed an increased yield of 94% and decreased isomerization (entry 10).^{13d, 13e, 20} Encouraged by these results, we elected to prepare a new triaryl phosphine ligand based on the 3,5-di-*tert*-butylarene.²¹ This ligand, DrewPhos (**L2**), consistently produced near quantitative yield and full suppression of isomerization (entry 11). Other silyl electrophiles (silyl chlorides, bromides, and triflates) were also investigated in the reaction, but were found to be much less reactive.^{22,23}

We believe the success of ligand **L2** is related both to its electron richness and its steric bulk. Steric bulk is known to promote reductive elimination.²⁴ In addition, the relative effectiveness of the triarylphosphine ligands examined in Table 1 directly correlates with their electron-richness, as judged by the ³¹P-⁷⁷Se coupling constants of the corresponding phosphine selenides.^{25,22} This correlation may imply a role of the ligand electron-density in slowing β-hydride elimination by stabilizing the palladium(II) alkyl intermediate relative to the palladium(II) hydride alkene complex.

To further improve the reaction, a single component (DrewPhos)₂PdI₂ catalyst was prepared. This precatalyst was highly efficient, allowing for a palladium loading as low as 1 mol % and complete reactions in as little as 1 h (Table 1, entry 12). Notably, this precatalyst is stable to air, moisture, and silica gel.

With catalytic conditions in hand, the scope of the zinc coupling partner was explored (Table 2). Model compound **1** was isolated in 93% yield. While the development of this method was focused on secondary nucleophiles, primary alkyl zinc iodides also coupled efficiently (**2**); however, in this case there was a modest background reaction (30%). With more sterically hindered primary reagents the background reaction was negligible, but the catalyzed coupling will still high yielding. Other cyclic zinc iodides can also be used (**4**).

Alkyl zinc bromides are generally less reactive than their iodide congeners, as exemplified by the near-negligible reactivity in the uncatalyzed reactions. However, under catalysis, these reagents also performed admirably using a 4 h reaction time (see Table 2, bottom).²⁶

The reaction is also scalable. Using isopropylzinc bromide, we isolated compound **1** on a multi-gram scale in near-quantitative yield.

Aliphatic, secondary zinc bromide substrates resulted in high yields (**7–9**). While the zinc insertion into bicyclic norbornyl bromide resulted in a 60:40 exo:endo ratio, the resultant silane was an 80:20 exo:endo mixture of **10**. We attribute this increase to the dynamic solution behavior of alkyl zinc bromides and differing reactivity between diastereomers.²⁷ The majority of commercially available zinc organometallic reagents are solutions in THF. Although THF is incompatible with silyl iodides,^{19b} solvent exchange of commercial α -methylbenzylzinc bromide solution and subsequent cross-coupling resulted in the isolation of **11** in 71% yield. This protocol greatly expands the pool of readily available nucleophiles in this transformation. Illustrating the robust nature of the catalyst and hindrance to β -hydride elimination, no styrene was detected in the formation of product **11**. Functionalized silanes were readily accessed with this methodology. Although alkenes proved incompatible,²² aryl chlorides, ethers, esters, and trifluoromethyls (**13–16**) were obtained in excellent yields. These functional groups allow for subsequent manipulation of the products.

Different substitution patterns on silicon allow for altered reactivity and downstream transformations.²⁸ In pursuit of a unified method to rapidly generate a diverse array of alkyl silanes, the scope of the silyl iodide coupling partner was explored (Table 3). The reaction provided excellent yields of trimethyl-, benzyldimethyl-, and methyldiphenyl silanes (**17–19**), demonstrating the flexibility of the system to adapt to changing steric and electronic environments around the silicon atom. Coupling sterically demanding triethylsilyl iodide resulted in a 30% yield of **20**. Although not high yielding, this is the first time that TES-I has participated in a palladium-catalyzed silyl electrophile cross-coupling.^{13e}

To further examine the steric limits of the catalytic system, the highly sterically demanding β,β -dimethyl and β,β,β -trimethyl substituted zinc iodide reagents were prepared and tested in the reaction (**21** and **24**, Figure 3). While the reactions required 15 h to go to completion, **21** led to **22** as a single regioisomer in 81% yield. The steric limitation of the system was realized, however, as the reaction of **24** provided a 56% yield of a 62:38 mixture of branched (**25**) and linear (**26**) isomers. Presumably, this occurs through β -hydride elimination and reinsertion to the sterically favorable terminal carbon atom. This demonstrates that even with severely strained, secondary neopentyl nucleophiles, β -hydride elimination is still not the predominant pathway.

Finally, this catalyst system is extremely robust. When run without precautions against air and moisture, the coupling reaction still produced **1** in 88% isolated yield (eq 1). This is remarkable for a palladium-catalyzed cross-coupling of this type.

(1)

In conclusion, we report a general palladium-catalyzed nucleophilic alkylation of silyl halide electrophiles with primary and secondary alkyl zinc halides. This transformation is amenable to various substitutions about the silicon center; allowing for diverse silane substitution on individual carbon frameworks. This work demonstrates the unique capabilities of the rationally designed DrewPhos catalyst to suppress isomerization and promote efficient cross-coupling. Paramount to this reactivity is the interplay of steric and electronic parameters of the DrewPhos ligand. While providing improved access to primary silanes, the reaction provides unprecedented access to secondary silanes using abundant silyl electrophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Long-Standing Challenge: Nucleophilic Alkylation of Silyl Electrophiles **State-of-the-Art: Umpolung Using Silyl Nucleophiles** **This Work: Silyl-Negishi Reaction (Natural Polarity)**

Figure 1.
Silane Alkylation Methods

Figure 2.
Proposed mechanism of silyl-Negishi reaction

Figure 3.
Examination of Steric Limits

Table 1Identification of Reaction Conditions^a

$ \begin{array}{c} \text{Me} \\ \\ \text{Me}-\text{C}-\text{ZnI} \\ \\ \text{Me} \end{array} \xrightarrow[\substack{\text{2 equiv Me}_2\text{PhSiI} \\ \text{1 equiv Et}_3\text{N} \\ \text{dioxane, rt, 4 h}}]{\substack{\text{2.5 mol \% [allylPdCl]}_2 \\ \text{10 mol \% Ligand}}} \begin{array}{c} \text{Me} \\ \\ \text{Me}-\text{C}-\text{SiMe}_2\text{Ph} \\ \\ \text{Me} \end{array} + \begin{array}{c} \text{Et} \\ \\ \text{CH}_2-\text{SiMe}_2\text{Ph} \end{array} $ <div style="display: flex; justify-content: space-around; width: 100%;"> 1 2 </div>			
entry	Ligand	1+2 (%) ^a	1:2 ^b
1 ^c	---	0	---
2 ^{d,e}	PPh ₃	31	95:5
3 ^d	PPh ₃	67	98:2
4	PPh ₃	77	99:1
5	(<i>o</i> -tol) ₃ P	48	98:2
6	(<i>p</i> -tol) ₃ P	91	>99:1
7	(<i>p</i> -CF ₃ C ₆ H ₄) ₃ P	42	87:13
8	(<i>p</i> -MeOC ₆ H ₄) ₃ P	88	>99:1
9	Ph ₂ P ^t Bu	83	93:7
10	JessePhos	94	98:2
11	DrewPhos	99	>99:1
12 ^f	(DrewPhos) ₂ PdI ₂	99	>99:1

^aYield determined by NMR;^bRatio determined by GC;^cNo Pd and ligand;^dRun with Pd₂dba₃·CHCl₃ in place of [allylPdCl]₂;^eEt₃N excluded.^f1.0 mol % Pd, 1 h.

Table 2

Scope of Zinc Reagent^{a,b}

$\text{R-ZnX} \xrightarrow[\text{1 equiv Et}_3\text{N, dioxane, rt, 1-4 h}]{\text{1 mol \% (DrewPhos)}_2\text{PdI}_2, \text{ 2 equiv Me}_2\text{PhSi}} \text{R-SiMe}_2\text{Ph}$	
Alkyl Zinc Iodides
1 93% (0%)	2 96% (30%)
3 95% (2%)	4 97% (0%)
Alkyl Zinc Bromides
1 98%, 4.35 g (0%)	5 91% (8%)
3 95% (3%)	6 97% (0%)
7 93% (0%)	8 94% (0%)
9 77% ^d (0%)	10 99% ^c (0%)
11 71% ^d (0%)	12 99% (0%)
13 81% (0%)	14 86% (0%)
15 94% (0%)	16 82% (0%)

^a Isolated Yields;^b Parenthetical yields run without catalyst, determined by NMR;^c exo:endo (80:20);^d Run for 16 h.

Table 3

Scope of Iodosilane^{a,b} ^a Isolated yields;^b Parenthetical yields run without catalyst, determined by NMR.